

THE RHOPALOCEPHALUS CARCINOMATOSUS.

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THE Memoirs on the parasites of cancer, published up to the appearance of the paper which forms the subject of this criticism, have been issued by scientists whose spurs have been won in pathological, rather than in zoological laboratories. It is true that Metchnikoff, in his review upon this subject,¹ has committed himself to a very definite opinion on this point, but his opinion was based more on the examination of the preparations of Soudakewitch and Ruffer, than on investigations of his own. Professor Korotneff's name being so well known in the zoological world, his opinion on such a question necessarily carries additional weight; but it is nevertheless permissible for one interested in pathological truth, and who has worked at this question, to examine, with care, the evidence upon which the alleged facts are founded. Aristotle, writing of science, declared that much learning produces much confusion (πολυμάθεια πολλάς ταραχάς ποιεῖ), but certainly, as regards the present work, no charge of confusion can be made, since the alleged facts are presented in the clearest and most categorical manner, leaving one in no doubt whatever as to the meaning conveyed; but one older than Aristotle has also stated that much learning does not teach wisdom (πολυμαθίη νόου οὐ διδάσκει), which seems to be borne out in the present instance, for it can hardly be said to be wise to publish so detailed, finished, clear, and complete an account as this of Dr. Korotneff's, from the examination of one single case of cancer.

After all, theories based on insufficient observation are very little removed from guesses; they soon fall to pieces, and their relics, as waste dust, are blown about for varying times, in the desert of scientific literature, and it sometimes looks as if this branch of investigation would be smothered in the dust of its own workshop.

The present Memoir, the first of a series of Monographs which Dr. Alexis Korotneff is writing upon "*Sporozoen als Krankheitserreger*," is entitled, "*Untersuchungen ueber den Parasitismus des Carcinoms*." When one reads a paper of this kind, containing a very elaborate and systematic account of a parasite of the gregarine species, said to have

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been found in a cancer, its development, and the various forms it assumes, in fact its complete biological history; and when, in Dr. Korotneff's first plate, the representation of the adult gregarine is given measuring $2\frac{3}{4}$ inches, with its tail curled up,—of whose existence he is so sure that he has christened it with a portentous title, corresponding in length to the figure mentioned above, namely, *Rhopaloccephalus carcinomatosus*,—it surely behoves anyone interested to examine, with the utmost accuracy and care, the evidence adduced.

In the first place, Dr. Korotneff appears to have examined only one case, and that one of epithelioma of the lip. We know that in epitheliomata more things difficult of exact interpretation are to be seen than in ordinary carcinomata; yet it seems hardly possible that one single case should be able to afford a secure foundation for the life-history of a parasite of this character. From a scientific point of view, it does not seem to me to be safe to speak so dogmatically of the appearances Dr. Korotneff describes, or to found thereon so elaborate and complete a life-history, without having made control observations upon more cases; neither do I think it can be called scientific to make up for this deficient observation, as Dr. Korotneff acknowledges he does, by saying that the greatest part of the drawings in the works of Soudakewitch, Sawtschenko, Kossinsky, Ruffer, and others, agree with his own, and that he can therefore judge of other cases besides his own. The drawings of Soudakewitch, and of Ruffer, certainly do not contain any images of any bodies resembling the *Rhopaloccephalus*, nor in those of Dr. Korotneff is there one figure resembling the parasites described by Soudakewitch or Ruffer, so that their drawings cannot in anywise be said to agree with Dr. Korotneff's. A careful comparison of these drawings will at once make this very evident.

Now as to Dr. Korotneff's methods. He fixes his tissue in a saturated solution of corrosive sublimate for a quarter to half an hour. Those who have tried this method (including myself) state that for any tissue this time is not long enough. It is sufficient to fix a film on a cover glass, but for any piece of tissue 12 to 24 hours is necessary; that is, in order to get a uniform fixation, otherwise only the margins are fixed, and this may lead to misinterpretations. In the case of pieces of tissue, the placing them directly into 70 per cent. alcohol is not so good a way as placing the pieces first into 30 per cent., then into 60 per cent., then into 90 per cent., and so on; which method causes far less distortion and shrinking of the cells. He uses generally Biondi's reagent for staining, otherwise gentian-violet and picric acid; which latter method I have specially tried, to see if my results agree with the specimens of the stain given by Dr. Korotneff in Plate I. Figs. 5–12, and of which I shall speak when discussing these figures.

With regard to Biondi's reagent, Dr. Korotneff says that it acts well after alcoholic fixation, but that when it is used after sublimate fixation only the nuclei of the lymphatic cells stain intensely green, and that

the nuclei of the cancer cells retain the red colour. This is wrong. In our hands, as well as in those of the greatest authority on Biondi's stain, namely Heidenhain, it most certainly is not the case. I have a great number of sections fixed in sublimate, in which the sublimate is not washed out with iodine, in which the nuclei of the cancer cells are everywhere green, the protoplasm orange red, and the fibrous tissue red, which is the real differentiation which this reagent should give. If the Biondi's solution does not give these characteristic reactions, something must be wrong; either the tissue is over-fixed with the sublimate, or is over-stained with the stain, or the sections are too thick, or the solution is no longer good; in any case, the absence of these definite reactions is a sign that some of the most elementary histological precautions have not been followed out. In some of Dr. Korotneff's specimens the nuclei of the leucocytes are red, although he himself states, as mentioned above, that the nuclei of lymphatic cells stain intensely green; again, in some of his pictures the protoplasm is pure orange in colour, which is never the case; it is an orange-red really. But if the common reactions of Biondi's solution do not occur, it is usually due to one of two of the causes mentioned above; either there is some fault with the solution, or the sections are too thick. This latter may be the case in this instance, as we read further on that his best results have been obtained from sections cut with the free hand from pieces of tissue not imbedded in anything. Considering the perfection of the present paraffin method, when carefully employed, this retrograde method of cutting sections without a microtome, or without imbedding, will not commend itself as tending towards accuracy in cases like this, where exact observation is an essential, especially when one considers the optical illusions, and the fallacies consequent thereon, which result from thick sections. If this reagent is used as it ought to be,—as Heidenhain, for instance, directs,—Dr. Korotneff cannot by any possibility get the differentiation of the various structures which he says he does, and therefore much of the basis of his theories must fall to the ground.

Next, as regards Dr. Korotneff's four pages of plates, containing 50 figures in all. For an original work of this kind the drawings or chromolithographs ought to be as nearly as possible copies of what is seen under the microscope, but no one ever saw such cells and nuclei as Dr. Korotneff depicts: "*ad nat.*" too. They are purely diagrammatic, mere outlines of cells and nuclei often, very coarsely done, and as such would do for the blackboard, but not for an original work of this character. Dr. Korotneff is also very careful not to mention in his description of the plates the method of staining employed; but as in the text, only the two methods mentioned above are detailed, it is presumable that the plates contain only specimens of these methods, and that Figs. 5-12, Plate I., are stained with gentian-violet and picric acid, and that all the rest from 1-50, with the exception perhaps of 13, are from Biondi-stained specimens. But the drawings are too primitive and diagrammatic,

even supposing them to be accurate, to be of any help in clearing up the mysteries of the paper; and even assuming that his technique is correct (which I have above shown it not to be), the paintings do not agree with his own description of what should follow from his methods. Were ever nuclei seen such as those, say, on Plate I.? These nuclei are bright red, and in Fig. 1 is a leucocyte (labelled so by Dr. Korotneff), the nucleus of which, even by Dr. Korotneff's own admission as to Biondi's stain, ought to be green instead of red, as printed. The "*Zooit*," or larval form in Fig. 1, is orange colour, nucleus and all, whereas in the adjacent figures they have bright red nuclei; in Fig. 13, again, the "*Zooit*" is entirely red; and in Fig. 20 it has a red nucleus and grey protoplasm; in Fig. 17, again, the nucleus of the "*Zooit*" is red and the protoplasm dark grey, whereas in Fig. 26 the protoplasm is again orange-coloured. The leucocytes also in Fig. 21 have red nuclei, and in Fig. 23 green, in Fig. 29 again red, and in Fig. 49 again green. In Fig. 15 is a "*Sporozooit*" coloured red, in Fig. 24 one orange-coloured, and in Fig. 21 one coloured grey, with a darker grey nucleus; in Fig. 33 one coloured grey with an orange nucleus; in Fig. 39, one red with a red nucleus; and in Fig. 36 two grey with yellow nuclei; and in Fig. 38 it is entirely orange. The "*Amœba*" form appears to be equally capricious as regards its staining reactions; sometimes its protoplasm is grey-green, as in Figs. 28, 29, 36, and sometimes bright red, as in Fig. 40. Cells can be seen in optical section, in most epitheliomata, shaped like the so-called gregarine in Fig. 2; and the so-called "*Zooits*" in Figs. 3 and 4 are invaginated cells. But Dr. Korotneff is silent as to cell invagination, also as to fragmentation of nuclei, also as to plasma cells and *Mastzellen*, the remembrance of the existence of all of which is very important when examining sections of cancer. Figs. 5-12 are stained with gentian-violet and picric acid, and are intended to show remarkable differentiations. I have prepared several sections precisely in the manner described, but have not been able to get this method to work with the diagrammatic or colour precision of Figs. 5-12; in fact, there is nearly as much difference between the actual and the represented gentian-violet and picric acid method, as there is between the actual and the represented Biondi method, a difference, as I have shown above, which is very great, in fact a different thing. In Figs. 9-11, even supposing the colour reactions to be as printed, Dr. Korotneff has, I think, let his imagination run riot; at any rate, in all these gentian-violet and picric-acid specimens, Figs. 5-12, some of the so-called "*Zooits*" may be equally well called leucocytes, or invaginated cells; and in Figs. 10 and 11, if the bodies in the centre of both cell-nests are parasites, as stated, why do the nuclei in Fig. 10 come out rose-red, and those in Fig. 11 blue?

In Fig. 13 is a coccidium stained red, both nucleus and protoplasm, and in the adjacent figures the coccidia appear with a red nucleus and a grey protoplasm. From Dr. Korotneff's description we

should expect them to be of a dark orange colour (*vide* p. 4). In Fig. 20 is a "Zooit" changing itself into a coccidium, and part of it is of a pale yellow colour; but why, and wherefore? The parasites seen in the centre of the cell-nests in Figs. 10, 11, and 21 are surely at variance with the experience of those who have observed such bodies in epitheliomata; they are, when present, only seen at the periphery of the cell-nests. The appearances seen in Figs. 23, 23 *bis*, 24, 29, 36, and 40, are simply prickles cells, the prickles of which, through hardening, etc., have shrunk away from those adjacent, and the cell-body having become condensed, the cell gets this amœbiform appearance. This I and others have seen, not only in epitheliomata, but in inflamed skin, in vaccinia for instance, and also in the inflamed cornea in man and animals. In Figs. 23, 25, and 43, one of the nuclei figured (there being supposed to be two in apposition) is printed blue. In all these cases they were in the specimens of the same presumably red colour, in which case it would be very difficult to separate them as figured, so as to be able to assert that they were in apposition. In Fig. 26 are figured a number of empty "Sporozooit" capsules "filled with leucocytes." But why are the leucocytes, or apparently one leucocyte, just in the centre of each capsule? Fig. 47 may be a good specimen of vacuolation; and many of the figures drawn in Figs. 48 *cc*, 49, 41-44 as parasites, are ordinary epithelioma cells; and Fig. 34, called an apposition of two coccidia, is probably a karyokinesis.

Many of these things mentioned above, and shown as parasites, can be seen even in normal skin, and most of them in skin, or cornea, which has been inflamed; they can also be seen in the skin in vaccinia, small-pox, and in chronic eczema, and they are certainly not in anywise typical of epithelioma. There is not in all these plates *one figure* resembling in any point those bodies described as parasites by Ruffer and Walker, and by Ruffer and myself, and by Soudakewitch, and which are found in epitheliomata with much difficulty. Soudakewitch has examined 4 cases of epithelioma, and at the Cancer Hospital I have examined 37 consecutive cases, and in *every case*, sometimes after prolonged search, I have found bodies such as are described by Soudakewitch and Ruffer. Dr. Korotneff states that any section from his case contains dozens of parasites, which is not to be wondered at, after what I have shown above, namely, that most of his parasites are epithelioma cells. Moreover, from the experience of this one case, Dr. Korotneff comes to the dogmatic but not scientific conclusion, nor one which is borne out by clinical observation, that cancer is only malignant when it contains the *Rhopalocephalus*; and this he puts at the head of his conclusions— "*Der Krebs ist eine verderbliche Geschwulst nur im Falle des Vorhandseins von Rhopalocephalus in seinem Innern.*" Surely the time was hardly ripe for such a conclusion; and if it had been, it would imply that cancer could exist in a non-malignant form, without the *Rhopalocephalus*, that is, we suppose, without the presence of a parasite, which, he asserts, stands in causal relationship to it, which is absurd.

One case is obviously not enough for all this; and I have shown that, as regards methods, the staining reagents have not the reactions Dr. Korotneff states they have, and that, even if they had, his drawings do not correspond to the results he maintains he gets; so that, on account of the number of cases examined being insufficient, on account of the methods of observation being inaccurate, and on account of the want of correspondence between the drawings and their description and interpretation, there can have been no true or logical basis established, out of which Dr. Korotneff can create such a creature as the *R. carcinomatosus*, with its zooites, sporozooites, and amœba forms.

After this review was written, I felt a certain amount of diffidence in sending it to the *Journal of Pathology*, as I feared I might be thought guilty of presumption in criticising the work of a worker in another branch of science. I took the liberty, therefore, of asking the opinion of Professor Metchnikoff, who from his great eminence as a zoologist, and having seen Dr. Korotneff's preparations, was well able to form an opinion on this point. He very kindly sent me the following criticism, which he allows me to append to this review:—

“I examined, in the spring of 1893, the preparations of Dr. Korotneff, and was very surprised at their imperfections. The pictures were entirely unclear, the staining quite diffuse, so that one could not rely at all on such preparations. Dr. Korotneff explained this on the ground that the sections (made without a microtome) were very thick, and did not allow of a differential staining. Under these circumstances it was impossible to determine anything with clearness in such preparations. One thing only can I assert with confidence, that Dr. Korotneff takes for parasites the pseudo-coccidia, which most certainly have nothing to do with parasites. With regard to his *Amœbæ*, etc., it is really impossible to judge, on account of the unclearness of the pictures. When one considers that these unclear pictures of Dr. Korotneff's refer to only one case, and that an epithelioma too (that is, one of those tumours least qualified for it), it will be easily understood that his opinion can only arouse the greatest scepticism.”¹

¹ “Ich habe im Frühjahr 1893 die Präparate Herrn Korotneff's gesehen, und war sehr überrascht durch ihre Mängelhaftigkeit. Die Bilder waren durchaus unklar, die Färbung ganz diffus, so dass man sich auf solche Präparate durchaus nicht verlassen könnte. Herr K. erklärte dies am dem Umstande, dass die Schnitte (ohne Microtom gemacht), sehr dickwaren, und eine Differenzialfärbung nicht zu liessen. Unter diesen Umständen war es unmöglich irgend etwas auf solchen Präparate mit Klarheit zu constatiren. Das eine kann ich nur mit Entschiedenheit behaupten, dass Herr K., als Parasiten die Pseudo-coccidien, welche ganz sicher nichts mit Parasiten zu thun haben, in Anspruch nimmt. Was seine ‘Amœben’ und dgl. betrifft, so ist es wirklich unmöglich, wegen die Unklarheit der Bilder, sich ein Urtheil darüber zu machen. Wenn man bedenkt, dass die undeutlichen Bilder Korotneff's sich nur auf einen Fall und dazu noch eines Epithelioms (*d.h.*, einer am wenigsten geeigneten Geschwulst) beziehen, so wird es leicht verständlich, dass seine Angaben nur den grössten Scepticismus erwecken können.”

(Signed) E. METCHNIKOFF.